Br J clin Pharmac 1994; **37**: 212–214

Population genetics of the angiotensin-converting enzyme in Chinese

EDMUND J. D. LEE
Department of Pharmacology, National University of Singapore, Singapore

A genetic polymorphism exists for the angiotensin-converting enzyme (ACE) gene which accounts for 44% of the variance of circulating ACE activity in a normal Caucasian population. The presence or absence of a 250 bp fragment in intron 16 of the gene serves as a marker for this polymorphism. One hundred and eighty-nine normal Chinese subjects were genotyped and phenotyped for this ACE polymorphism. The frequencies of the deletion and insertion alleles among Chinese are 0.3 and 0.7 respectively, indicating a much higher prevalence of the insertion allele than had been reported among Caucasians.

Keywords genetic polymorphism angiotensin-converting enzyme ACE Chinese

Introduction

Angiotensin-converting enzyme (ACE) is a dipeptidase which is responsible for the conversion of angiotensin I to angiotensin II. Although ACE is primarily a membrane bound enzyme, significant ACE activity can be found in the circulation. The ACE gene is 21 kilobases long and consists of 26 exons [1]. Extensive homology between exons 4–11 and 17–24 is suggestive of previous gene duplication. A large ACE is found in the endothelium and most other tissues, and is encoded for by exons 1–26 excluding exon 13. Testicular ACE is however, smaller, and is encoded for by exons 13–26. Alternate promoters for the two enzymes are found in the 5′-flanking region of exon 1 as well as in exon 12.

A genetic polymorphism has been described in intron 16 of the ACE gene [2]. Individuals varied as to the presence (insertion, I) or absence (deletion, D) of a 287 bp fragment. It has been estimated that the ID polymorphism accounts for about 28% of the variance in ACE activity in a normal Caucasian population [2]; presence of the I allele being associated with higher circulating ACE activity. An association of the homozygous I genotype with hypertension has been reported [2, 3], although this has recently been disputed [4]. The DD genotype, on the other hand, may be an important risk factor in patients who are otherwise at low risk for coronary artery disease [4]. Since the insertion (I)/deletion(D) mutation occurs in an intronic region it is unlikely that the mutation results in changes in the coded enzyme. It has consequently been postulated that the I allele existed in linkage disequilibrium with an as yet unidentified ACE gene variant. Combined segregation and linkage analyses estimated that this gene variant might account for 44% of circulating ACE activity [2].

The frequency of the I allele and that of the unknown gene variant in a normal Caucasian population has been estimated to be 0.43 and 0.56 respectively. This is the first description of the ACE genetic polymorphism in a Chinese population.

Methods

One hundred and eighty-nine normotensive subjects were recruited from within the undergraduate population as well as from the National University Hospital Blood Transfusion Unit. The subjects were selected because they had no known history of hypertension and if they had a casual blood pressure reading of less 130/90 mm Hg. Blood samples (5 ml) were collected in heparinised vacutainer tubes. Genomic DNA for genotyping was extracted from a 50 μl aliquot of whole blood. After centrifugation, the plasma fraction was stored at −20° C until the assay for ACE activity could be performed.

Presence of the I and D alleles was detected by polymerase chain reaction (PCR) [5]. ACE activity in plasma was measured by a fluorimetric method using hippuryl-L-histidyl-L-leucine as substrate [6]. Activity was expressed as nmol of L-histidyl-L-leucine formed min^{-1} ml^{-1} of plasma.

Correspondence: Dr Edmund J. D. Lee, Associate Professor, Department of Pharmacology, National University of Singapore, Kent Ridge, Singapore 0511

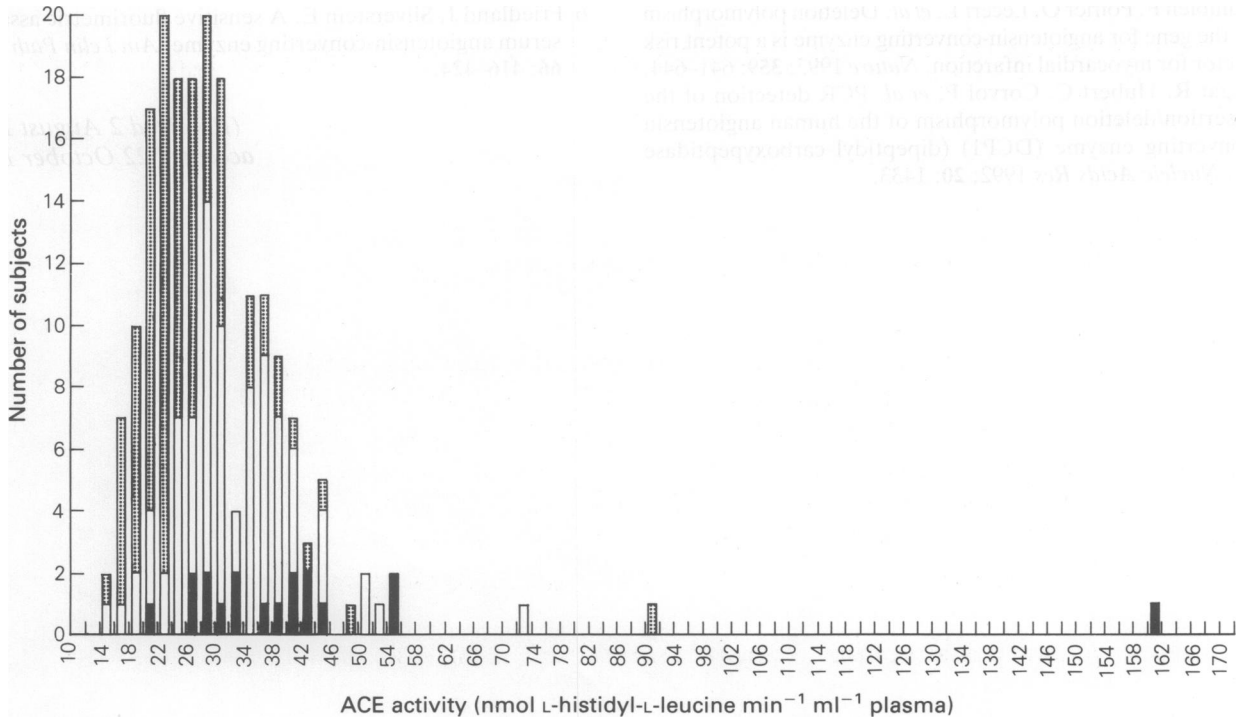

Figure 1 Frequency histogram of plasma ACE activity in the DD, ID and II genotypes among 189 Chinese. ⊠ homozygous I, □ heterozygous, ■ homozygous D.

Results

Of the 189 subjects, 18 were homozygous for the D allele, 94 homozygous for the I allele and 77 were heterozygotes. These proportions were consistent with the *Hardy-Weinberg* equilibrium, which predicted frequencies of D and I alleles in the population to be approximately 0.3 and 0.7 respectively. The median (and range) of ACE activity in the DD, ID and II genotypic groups were 37.7 (21.4–160.5), 31.5 (15.4–72.9) and 24.4 (14.8–90.56) nmol L-histidyl-L-leucine min^{-1} ml^{-1} plasma respectively (Figure 1). The mean ACE activity for each genotype was significantly (two-tailed Wilcoxon rank sum test, $P < 0.05$) different from each other.

Discussion

Although significant ACE activity can be found in the circulation, the origins and functional relevance of this circulating ACE have not been clearly established. It is generally believed however, that ACE is primarily important at the tissue level. Nevertheless, the amount of circulating ACE appears to be determined, at least in part, by the I/D genetic polymorphism. Our study has confirmed this correlation in a normotensive Chinese population. However, the considerable overlap in ACE activity between the genotypes suggests the presence of other, possibly non-genetic, determinants of circulating ACE. The frequency of the I allele among Chinese is considerably higher than that described in a French population. More studies are required to see if this is translated into altered risks of coronary artery disease and hypertension amongst Chinese.

This study was supported by NUS grant RP 870317. I wish to thank Mr David Yue, Miss S. M. Yeong and Mr S. B. Ang for technical assistance; as well as staff of the NUH Blood Transfusion Unit.

References

1 Hubert C, Houot A-M, Corvol P, *et al.* Structure of the angiotensin I-converting enzyme gene: Two alternate promoters correspond to evolutionary steps of a duplicated gene. *J biol Chem* 1991; **266**: 15377–15383.

2 Tiret L, Rigat B, Visvikis S, *et al.* Evidence, from combined segregation and linkage analysis, that a variant of the angiotensin I-converting enzyme (ACE) gene controls plasma ACE activity. *Am J hum Genet* 1992; **51**: 197–205.

3 Zee RYL, Lou Y-K, Griffiths LR, *et al.* Association of a polymorphism of the angiotensin I-converting enzyme gene with essential hypertension. *Biochem Biophys Res Comm* 1992; **184**: 9–15.

4 Cambien F, Poirier O, Lecerf L, *et al.* Deletion polymorphism in the gene for angiotensin-converting enzyme is a potent risk factor for myocardial infarction. *Nature* 1993; **359**: 641–644.
5 Rigat R, Hubert C, Corvol P, *et al.* PCR detection of the insertion/deletion polymorphism of the human angiotensin converting enzyme (DCP1) (dipeptidyl carboxypeptidase 1). *Nucleic Acids Res* 1992; **20**: 1433.
6 Friedland J, Silverstein E. A sensitive fluorimetric assay for serum angiotensin-converting enzyme. *Am J clin Path* 1976; **66**: 416–424.

(Received 2 August 1993, accepted 22 October 1993)